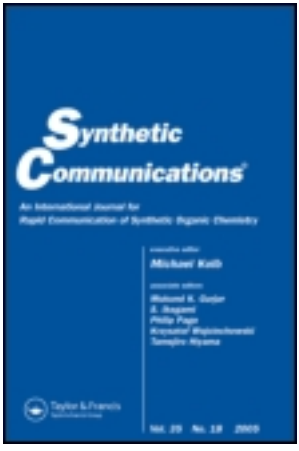

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Microwave-Assisted Phenothiazines Preparation by Thionation of Diphenylamines

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MICROWAVE-ASSISTED PHENOTHIAZINES PREPARATION BY THIONATION OF DIPHENYLAMINES

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ABSTRACT: A preparation in 'dry media' of phenothiazine derivatives by thionation of diphenylamines using microwave-activation is presented. This method allowed the preparation of 2,4,6,8-tetra-tert-butyl-10*H*-phenothiazine **2e**, the first 2,4,6,8-tetra-substituted derivative of this heterocycle, practically inaccessible by other thionation procedure.

The application of microwave activation in organic synthesis has been known to have significant advantages [1-4]. Organic reactions carried out in dry media have been widely used [5]. The coupling of these two technique, the use

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of microwave irradiation and ' dry media ', has attracted much attention[6].

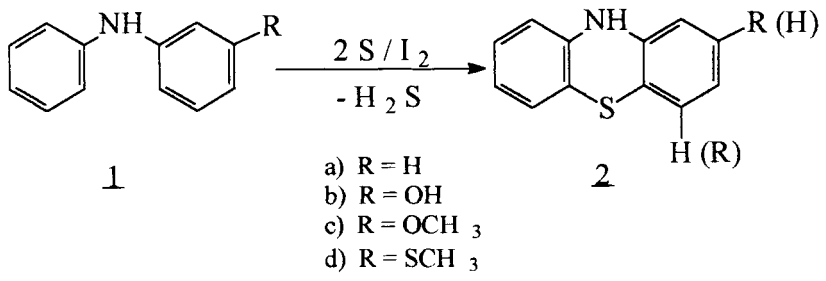
It is well known [7] that the most useful general method for preparing phenothiazines is the ring closure of the corresponding diphenylamines using sulphur as reagent and iodine as catalyst. This method is sometimes tedious and it is often accompanied by degradation reactions. In order to alleviate these inconvenients we tried to change this method by absorbing the reagents (diphenylamines and sulphur) on an inorganic solid support, namely, alumina, and by replacing conventional heating with microwave irradiation as an activation procedure.

Our treatment precinct is an original one and consists of a parallelipipedic microwave-cavity, as we presented in the previous paper [8].

We started our studies with the thionation of diphenylamines on the above mentioned solid support. Besides its specific action on the reaction due to the chemosorption of reagents, alumina was used for concentrating the electromagnetic field in the substrate. However, in order to obtain better yields, an alternative procedure using no adsorbent was developed.

The structure for the new product **2e** was identified by MS measurements, ^{1}H-NMR (see **Experimental**) and X-ray diffraction on single crystals (will be published elsewhere).

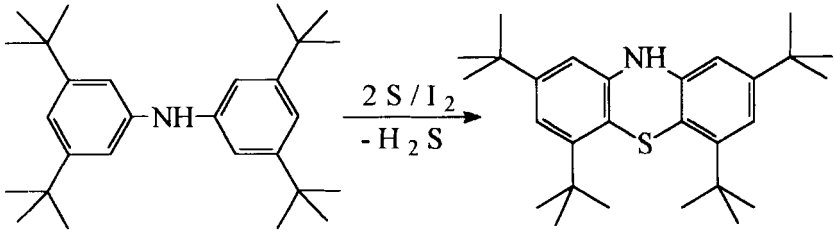
The microwave-assisted preparation of phenothiazines was achieved according to the following scheme:



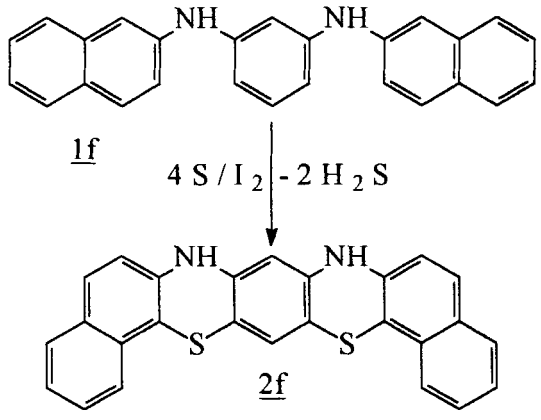
1

a) R = H
b) R = OH
c) R = OCH 3
d) R = SCH 3

2



1e 2e



2f

The results of our experiments are shown in Table. Our data show that solid-state preparation of phenothiazines using microwaves is extremely convenient from the practical viewpoint. Without the solid inorganic support (alumina), the thionation reaction of diphenylamines with sulphur is faster and the yields are better, since on

alumina there is an irreversible adsorption of the product after microwaves treatment. The absence of solvent coupled with the high yields and very short reaction times make this procedure for phenothiazines preparation very attractive.

EXPERIMENTAL

The reactions were performed in a quartz open vessel. The reactions were monitored by TLC on "MERCK" silicagel 60 F 254 plates eluting with toluene or 9:1 toluene:acetone mixture; the visualization was done using a 254 nm UV lamp. The best ratio of diphenylamine to solid support was proved to be 5 mmol/5g, with the stoechiometric amount of sulphur and 1% iodine. The identity of compounds **2a-d** and **2f** was checked-up by elemental analyses and confirmed by comparison of TLC of these compounds with those of authentic samples. The following apparatus were used: NMR, VARIAN GEMINI 300, spectrum was recorded in acetone-D6 and chemical shift are given in ppm with TMS signal at 0 ppm; MS, VARIAN MAT 311, operated at an electron energy of 70 eV.

General procedure for preparation of compounds 2a-2f.

1. Diphenylamines **1** (5mmol), the stoechiometric amount of powdered sulphur and 1% quantity of iodine were dissolved into a minimum volume of acetone and absorbed on MERCK Alumina 70-230 mesh ASTM (5g). The solvent was then evaporated and the dry mixture was irradiated with microwaves (see Table). The resulting phenothiazines **2** were extracted from the support with the proper boiling solvent, as follows:

Product	Solvent used for extraction
10*H*-Phenothiazine **2a**	Ethanol
10*H*-2- and 10*H*-4-Phenothiazinol **2b**	Benzene
2- and 4-Methoxy-10*H*-Phenotiazine **2c**	Acetone
2- and 4-(Methylthio)-10*H*-Phenothiazine **2d**	Acetone
2,4,6,8-tetra-tBu-10*H*-Phenothiazine **2e**	Benzene
16*H*,18*H*-Dibenzo[c,l]-7,9-ditia-16*H*,18*H*-diazapentacene **2f**	Dimethylformamide

The compounds **2a**, **2b**, **2e** and **2f** were purified by recrystallization from the same extraction solvent. For purification of **2c** and **2d** the acetone was evaporated at room temperature and the residue was purified by recrystallization from benzene. The 4-OH and 4-SMe isomers of **2b** and **2d** were not isolated. The isomers of **2c** were isolated by column cromatography on neutral alumina. The eluting solvent was toluene. Pure products were obtained after crystallisation. Melting points are presented in Table.

The new compound **2e** was characterised by MS: m/e (intensity %) 423 (80) M^+, 57 (35) M^+- 366 (t-Bu), and ^{1}H-NMR δ (ppm): 0.85 (36H), 8.10 (4H), 8.20 (1H).

2. Diphenylamines **1** (5mmol), the stoechiometric amount of powdered sulphur and 1% quantity of iodine were mixed and placed in an opened quartz vessel and irradiated with microwaves. The work-up was carried out as is indicated above (see **General procedure 1**), excluding the extraction step.

The resulting hydrogen sulphide was neutralized by bubbling through a NaOH solution.

Table. Phenothiazines prepared by microwave irradiation at 700 W (2.45GHz).

Reagent	Product	Conventional		M.p. (Lit. m.p.) °C	Lit.	Microwave			
						with alumina as support		without alumina as support	
		Time (min)	Yield (%)			Time (min)	Yield (%)	Time (min)	Yield (%)
Diphenylamine **1a**	10H-Phenothiazine **2a**	90	85-90	171 (170-171)	*9*	7	80	3	90
3-Hydroxy-diphenylamine **1b**	10H-2-Phenothiazinol : 10H-4-Phenothiazinol **2b**	30	89 1:0 [a,b]	272-273 (270-272)	*10*	7	62 [c]	2	65 [c]
3-Methoxy-diphenylamine **1c**	2-OMe-10H-Phenothiazine : 4-OMe-10H-Phenothiazine **2c**	60	48 1:0 [a,c]	186-187 (185-188) 99-100 (98-99)	*11*	10	58 17:3 [a]	1.3	60 30:2 [a]
3-(Methylthio)-diphenylamine **1d**	2-SMe-10H-Phenothiazine : 4-SMe-10H-Phenothiazine **2d**	285	94 1:0 [a,c]	137-138 (136)	*12*	10	59 [c]	0.8	82 [c]
3,5,3',5'-tetra-tBu-diphenylamine **1e**	2,4,6,8-tetra-tBu-10H-Phenothiazine **2e**	-	-	98-99	-	20	5	8	50
N,N'-bis-(β-naphthyl)-m-phenylenediamine **1f**	16H,18H-Dibenzo[c,l]-7,9-dithia-16H,18H-diazapentacene **2f**	30	70	292 (290)	*13*	10	70	1	89

[a] Molar ratio of the resulting isomers
[b] 10H-Phenothiazin-4-ol was obtained from Phenothiazine-5-oxide (ref. 10)
[c] The 4-OH and 4-SMe isomers were not isolated

CONCLUSIONS

The above microwave-assisted phenothiazine preparations demonstrate once more that a great simplification of procedure can be achieved. The protocol using no inorganic solid support for activation of thionation of diphenylamines under focused microwave irradiation affords a clean, efficient, and selective method.

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REFERENCES

1. Bram G., Loupy A., Villemin D., in "Solid Support and Catalysts in Organic Synthesis", Edit. Ellis Horwood, PTR Prentice Hall, Londres, vol. XII, **1992**, pp.302;
2. Loupy A., *Spectra Analyse*, **1993**, 33;
3. Majetich G., Hicks R., *Phys. Radiat. Chem.*, **1995**, *45*, 567;
4. Caddick S., *Tetrahedron*, **1995**, *51*, 10403;
5. Laslo P., *Acc. Chem. Res.*, **1986**, *19*, 121 and references cited therein

6. Baghurst D.R., Mingos D.M.P., *J. Chem. Soc. Chem. Commun.*, **1985**, 829; Baghurst D.R., Mingos D.M.P., *J. Chem. Soc. Chem Commun.*, **1988**, 829; Baghurst D.R., Mingos D.M.P., *J. Organomet. Chem.*, **1990**, *C57*, 384; Baghurst D.R., Cooper S.R., Greene D.L., Mingos D.M.P., Reynolds S.M., *Polyhedron*, **1990**, *9*, 893; Greene D.L. and Mingos D.M.P., *Transition Metal Chem.*, **1991**, *16*, 71; Whittaker A.G., Mingos D.M.P., *J. Chem. Soc. Dalton Trans.*, **1993**, 2541; Dabirmanesh Q., Roberts R.M.G., *J. Organometallic Chem.*, **1993**, *C28*, 460; Mingos D.M.P., Baghurst D.R., *Chem. Soc. Rev.*, **1991**, *1*, 20; Mingos D.M.P., *Res. Chem. Intermed.* **1994**, *20*, 85; Mingos D.M.P., *Chem. & Ind.*, **1994**, 596

7. Bodea C., Silberg I.A. ,"Recent advances in the chemistry of phenothiazines", Academic Press Inc., New York, USA, **1968**

8. Filip S.V., Surducan E., Vlassa M., Silberg I.A., Jucan G., *Heterocyclic Commun.*, **1996**, *2*, 431-434

9. Wunderlich H., **1961**, *Ger (East) Patent* 20, 104; *Chem. Abstr.* **1962**, *56*, P 477h; Britton E.C., Eiseman J.E., **1942**, *U.S. Patent* 2,295-074; *Chem. Abstr.*, **1943**, *37*, 892[5]

10. Fujimoto M., *Bull. Soc. Chem. Japan*, **1959**, *32*, 371-372; Nodiff E.A., Lipschutz S., Craig P.N., Gordon M., *J. Org. Chem.*, **1960**, *25*, 60-65

11. Kadaba P.K., Massie S.P., *J. Org. Chem.*, **1959**, 24, *986-987*; Cymerman-Craig J., Rogers W.P., Tate M.E., *Australian J. Chem.*, **1957**, *9*, 397-405

12. Terdic M., Pasnicu V., **1978**, *Rom. Patent* 63983; Société des usines chimiques Rhône-Poulenc, **1958**, *Brit. Patent* 802,726; *Chem. Abstr*, **1959**, *53*, 7209d

13. Silberg I.A., Cristea C., *Heterocyclic Commun.*, **1996**, *2*, 117-124

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